UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,743	06/10/2002	Brett P Monia	RTSP-0234	6022

26259 7590 12/02/2004

LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,743	MONIA ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Jan. 10, 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's preliminary amendment October 3, 2002 has been fully entered, claims 16-19 are pending, and are examined herein below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on January 10, 2002 was filed before the mailing date of the instant first action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner, and is attached herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of PI3 kinase p110 delta, SEQ ID NO: 1 expression *in vitro*, does not reasonably provide enablement for methods of treating diseases associated with the expression of PI3 kinase p110 delta *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to methods of treating an animal having a condition associated with PI3 kinase p110 delta (SEQ ID NO: 1), wherein said compositions are administered to animals such that expression of PI3 kinase p110 delta is inhibited, wherein said condition may be an inflammatory disorder, which itself may be asthma or rheumatoid arthritis.

The specification teaches prophetic methods of treatment using antisense oligos targeted to PI3 kinase p110 delta, with broad treatment regimens that include pharmaceutical formulations, and treatment regimens comprising antisense administration at concentrations between 0.01 μg to 100 g per kg of body weight, from once or more daily to once every 20 years. The specification provides exemplifies only for methods of using the claimed compositions to inhibit the expression of PI3 kinase p110 delta in cultured cells *in vitro*.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is unpredictable. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) review article by Braasch et al. concludes that major obstacles persist in the art of using antisense oligos in treating disease: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. specifically identify 3 factors that contribute to the unpredictable efficacy of using antisense compounds in general: 1) the variable capability of antisense oligonucleotides to access sites within the mRNA to be targeted; 2) problems pertaining to the delivery and uptake of the antisense oligos by cells, with the result that "the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death"; and 3), that "oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. elaborates, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents,

Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target, and that "[a]ttempts to describe the *in vivo* structure of RNA, in contrast to DNA, have been fraught with difficulty." (Page 3161, second column).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379). Gewirtz adds that [t]he other major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their target . Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient."

Branch et al. discuss the problems pertaining to non-specific oligo interactions that lead to artifactual phenotypes during *in vivo* antisense administration: "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the

immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, regarding the therapeutic benefit of antisense technology in general, Branch states that "in fact, nucleic acid drugs should not be thought of as magic bullets. Their therapeutic use will require vigilant monitoring. Compared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs extend only across a narrow concentration range. Both *in vitro* and *in vivo*, less than a factor of ten often separates the concentration producing no antisense effect form that producing the full antisense effect. Steep dose-response curves commonly indicate that a drug has multiple, synergistic mechanisms of action. A drug with a narrow therapeutic window can be potent and extremely valuable, but can also be tricky to use safely. Since the ratio of antisense to non-antisense effects drops sharply outside a restricted concentration range, it will be challenging to obtain consistent therapeutic benefit (Page 46, second column).

Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

Finally, Branch states that "[i]t is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers will identify ODNs that are effective *in vivo*. With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy, straightforward new screening techniques need to be developed for use in cells."

Thus, it is maintained that the prior art at the time of applicants' filing would not enable claims directed to the therapeutic use of antisense oligos directed to PI3 kinase p110 delta *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of *in vitro* examples and broad prophetic treatment regimens enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

This is particularly true in view of the claimed breadth of claim 16, which is drawn broadly to treating or preventing any condition or disease suspected of being associated with PI3 kinase p110 delta (SEQ ID NO: 1) *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the antisense administered, and specifically regarding the instant compositions and methods claimed.

Since the specification fails to provide any real guidance for the methods of using antisense *in vivo* or in the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those sequences that are successfully delivered to target sites in appropriate

cells and /or tissues such that inhibition is achieved and treatment attained. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Prior Art Relevant to the Instant Disclosure

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Van Hasebroeck *et al.* (WO 97/46688) is considered relevant to the instant claims, particularly claim 16, which is drawn broadly to methods of treating a human having a disease associated with PI3 kinase p110 delta of SEQ ID NO: 1 comprising administering antisense directed to PI3 kinase p110 delta.

Van Hasebroeck *et al.* teaches a method of administering antisense oligos 20 to 30 nucleotides long targeted to PI3 kinase p110 delta, wherein the PI3 kinase p110 delta target of Van Hasebroeck consists of 3387 nucleotides out of the 3868 nucleotide target of PI3 kinase p110 delta of applicant's instant SEQ ID NO: 1. However, disregarding the extra nucleotides of applicants instant SEQ ID NO: 1, the 3387 nucleotide sequence of Van Hasebroeck is otherwise identical in sequence to SEQ ID NO: 1 (see attached alignment), and thus any antisense oligo of Van Hasebroeck would anticipate the instant claims.

However, the disclosure of Van Hasebroeck is considered to be lacking enablement for the same reasons as applicants instant disclosure; namely, the prior art is not considered enabling for methods of treatment using antisense oligos, and Van Hasebroack has provided mere prophetic guidance and *in vitro* examples that are not considered to overcome the known

unpredictability of antisense-based therapeutic treatment, thus requiring one of skill in the art to engage in undue trial and error experimentation in order to practice the claimed method.

Support for this conclusion comes from M.P.E.P. 2121.01 [R-2]:

> "USE OF PRIOR ART IN REJECTIONS WHERE OPERABILITY IS IN QUESTION"
> "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention not novel' or anticipated' within section 102, the stated test is whether a reference contains an enabling disclosure'... ." In re Hoeksema, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). *>**The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation.** Elan Pharm., Inc. v. Mayo Foundation for Medical and Education Research, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003) (At issue was whether a prior art reference enabled one of ordinary skill in the art to produce Elan's claimed transgenic mouse without undue experimentation. Without a disclosure enabling one skilled in the art to produce a transgenic mouse without undue experimentation, the reference would not be applicable as prior art.).< A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). (Emphasis added)

Accordingly, the disclosure of Van Hasebroeck is relied upon but not cited as art under 35 U.S.C. § 102.

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

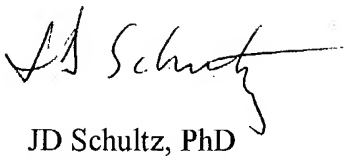
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

JDS



JD Schultz, PhD
Patent Examiner
Art Unit 1635